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Amide-Forming Ligation of Acyltrifluoroborates and Hydroxylamines in Water**

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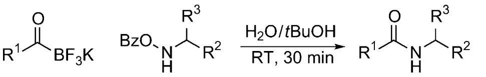
Amides are among the most prevalent organic functional groups, especially as components of natural products and pharmaceuticals and as the backbone of peptides.[1,2] The most common means of preparing amides is the dehydrative coupling of amines with carboxylic acids, but the need to fully protect other functional groups and to employ excess amounts of coupling reagents renders it increasingly unattractive in comparison to a new generation of bond-forming reactions. Carbon–carbon bonds, for example, are now routinely prepared from prefunctionalized reagents, such as boronic acids, using operationally simple and catalytic conditions, which tolerate unprotected functional groups. Amide-forming reactions that meet these strict criteria have the potential to facilitate small-molecule drug discovery and enable chemoselective bioconjugation reactions. Our group and others have therefore sought to identify mechanistically unique amide-forming reactions from precursors other than amines and carboxylic acids.[3–7]

As part of our continuing efforts towards this goal we now disclose a rapid and remarkably simple amide-forming ligation using acyltrifluoroborates and *O*-benzoyl hydroxylamines [Eq. (1); Bz = benzoyl]. This chemoselective amidation occurs in water at room temperature without the need for reagents or catalysts. These reactions represent a new approach to amide formation and establish acyltrifluoroborates as robust, synthetically useful reagents that serve as prefunctionalized monomers for predictable cross-coupling reactions.

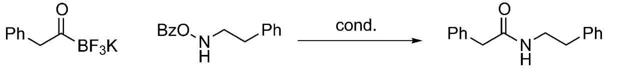


(1)

Our discovery arose from the combination of our interest in new amide-forming ligations and our previous synthesis of acyltrifluoroborate **1a**.[8] It was also reported that **1a** reacts with azides in an HBF_4-promoted process to form amides. This transformation is related to the elegant work of Matteson and Kim on the preparation of secondary amines from alkyldihaloboranes and azides.[9] This amide-forming reaction had limitations in the form of a narrow substrate scope and the need for a strong fluorophilic reagent. We hypothesized that acyltrifluoroborates could instead serve as surrogates for α-ketoacids in amide-forming ligations with hydroxylamines.[10] We found that *O*-unsubstituted hydroxylamines reacted with acyltrifluoroborates to give stable nitrones rather than amides.[11] In contrast, and disclosed herein, *O*-benzoyl hydroxylamines[12] underwent rapid amide formation in aqueous solvents without the need for reagents or catalysts.

Our initial studies were performed using phenylacetyl trifluoroborate (**1a**) and *O*-benzoyl hydroxylamine **2a**. A solvent screen, in which the reactions were performed in the presence or in the absence of oxalic acid, revealed that aqueous mixtures were particularly well suited for the reaction (Table 1). In contrast to the reaction of α-ketoacids, reactions performed in polar aprotic solvents such as DMSO and DMF, in the absence of water or acid, were ineffective

Table 1: Solvent screening for the ligation of acyltrifluoroborate **1a**.[a]



1a **2a** **3a**

Entry	Conditions	*T* [°C]	[**1a**]	Result
1[b]	$[D_6]$DMSO or DMF	40	0.1 M	No reaction
2[b]	DMF, $(CO_2H)_2$ (1 equiv)	40	0.1 M	90% conversion of **1a**
3	THF	RT	0.1 M	**1a** not soluble
4	7:3 THF/H_2O	RT	0.1 M	Full conversion of **1a** after 30 min
5	MeOH	RT	0.1 M	Methanolysis of **2a**
6	1:1 H_2O/*t*BuOH	RT	0.1 M	Full conversion of **1a** after 15 min
7	1:1 H_2O/*t*BuOH, $(CO_2H)_2$ (1 equiv)	RT	0.1 M	Full conversion of **1a** after 15 min
8[c]	1:1 H_2O/*t*BuOH	RT	0.01 M	Full conversion of **1a** after 30 min
9	1:1 LB medium/*t*BuOH (protein digests)	RT	0.1 M	Full conversion of **1a** after 15 min

[a] **1a** (0.05 mmol), **2a** (0.055 mmol), solvent (0.5 mL), 30 min. [b] Reaction time of 6 h. [c] Reaction time of 1 h; 5 mL of solvent. DMF = dimethylformamide, DMSO = dimethyl sulfoxide, LB = lysogeny broth, THF = tetrahydrofuran.

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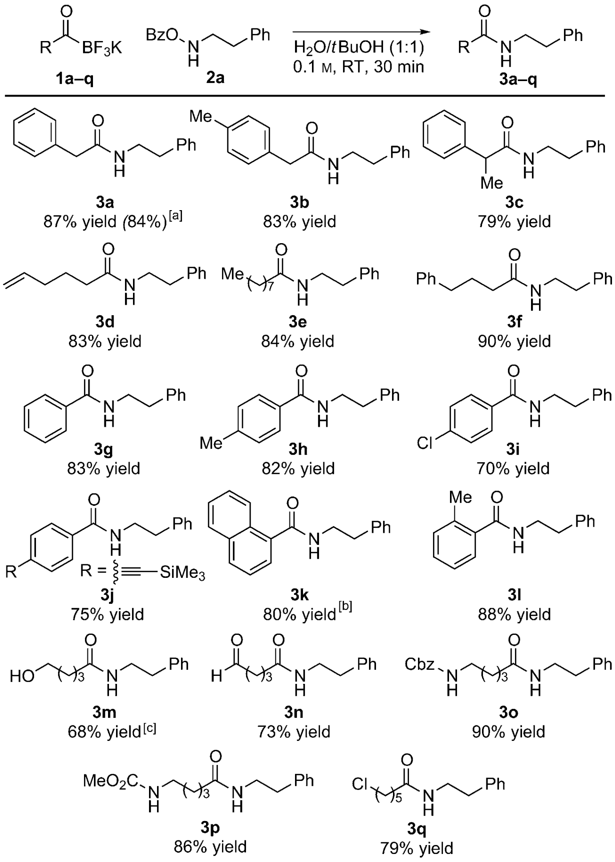
(Table 1, entry 1). In some cases, the insolubility of the trifluoroborate prevented the reaction, as in THF for example (Table 1, entry 3); however, in aqueous THF, in which the acyltrifluoroborate was soluble, the ligation proceeded cleanly (Table 1, entry 4). Our preferred solvent system was 1:1 H_2O/*t*BuOH because the acyltrifluoroborate was soluble and the reaction was rapid and clean, with full conversion being achieved within 15 minutes at room temperature at 0.1M substrate concentration (Table 1, entries 6 and 7). Even upon dilution of the reaction mixture by 10-fold, full conversion of the acyltrifluoroborate was observed within 30 minutes at 23 °C (Table 1, entry 8). A ligation performed in a solution of protein digests (LB medium, $10\,\mathrm{mg\,mL^{-1}}$ in peptide fragments) occurred smoothly, thus indicating that the ligation can be performed in the presence of unprotected functional groups and is chemoselective (Table 1, entry 9).

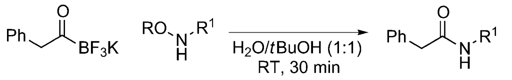
The ligation was remarkably general with respect to the acyl donor; all acyltrifluoroborates subjected to the reaction thus far have given the expected amide product in good yield (Scheme 1). Monitoring the reactions by LC/MS indicated that complete conversion was often achieved in less than 5 minutes at 0.1M; the experiments were allowed to run for 30 minutes in the interests of convenience. Bulky 1-naphthoyltrifluoroborate (**1k**) was the only substrate that required longer reaction times (1 hour). In the phenylacetyl series, both α-unsubstituted (**1a** and **1b**) and branched substrates (**1c**) reacted to form amides within the same amount of time (30 minutes at 23 °C). Alkyl-substituted acyltrifluoroborates, even those with long hydrocarbon chains, such as **1e**, were also fully soluble in the aqueous solvent; this solubility is attributable to the high polarity of the trifluoroborate moiety. Benzoyltrifluoroborates **1g–l** were also excellent reaction partners; in contrast, the corresponding α-ketoacids reacted sluggishly. The reaction was compatible with the presence of unprotected alcohols (**3m**), aldehydes (**3n**), carbamates (**3o** and **3p**), and alkyl chlorides (**3q**).

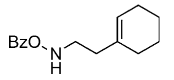
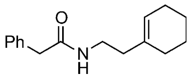
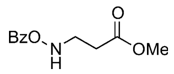
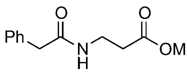
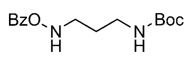
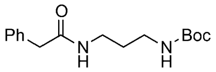
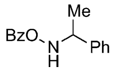
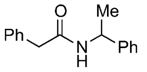
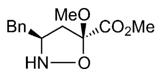
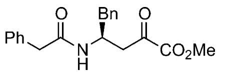
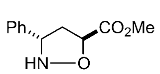
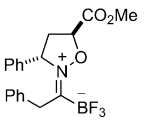
A preliminary evaluation of a series of *O*-benzoyl hydroxylamines showed that the reaction was also general with respect to this substrate (Table 2). Ligation with cyclohexenyl-containing hydroxylamine **2b**, designed as a mechanistic probe for nitrone intermediates,[13] gave amide **3r** cleanly (Table 2, entry 1). Compatibility of the reaction with esters and carbamate-protected amines, which is important for future extensions of this method, was demonstrated by the reactions of **2c** and **2d**. Branched amine **2e** was unreactive



Scheme 1. Ligation of acyltrifluoroborates with *O*-benzoyl hydroxylamine **2a**. Reaction conditions: acyltrifluoroborate (0.10 mmol), **2a** (0.11 mmol), 1:1 H_2O/*t*BuOH (1 mL), RT, 30 min. [a] Yield in parentheses is for reaction performed in 1:1 LB medium/*t*BuOH. [b] Reaction time of 1 h. [c] After 30 min at RT, reaction warmed to 60 °C for 30 min. Cbz = benzyloxycarbonyl.

Table 2: Ligation of **1a** with *O*-benzoyl hydroxylamines and isoxazolidines.[a]

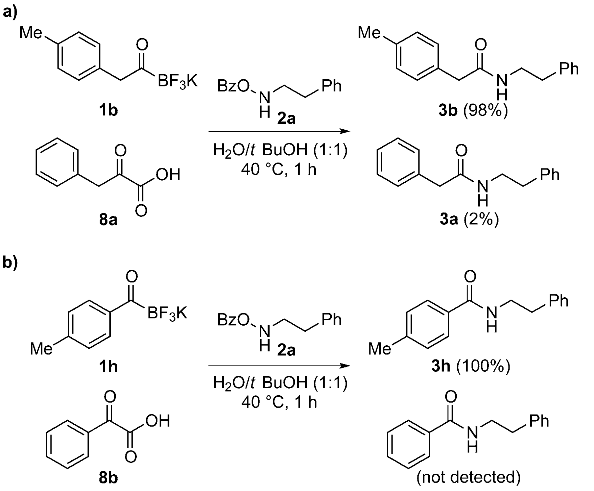


Entry	RO-NHR^1	Product	Yield [%]
1	 **2b**	 **3r**	82
2	 **2c**	 **3s**	90
3	 **2d**	 **3t**	96
4[b]	 **2e**	 **3u**	79
5[b,c]	 **4**	 **5**	88
6[d]	 •HCl **6**	 **7**	99

[a] **1a** (0.10 mmol), RONHR^1 (0.11 mmol), 1:1 H_2O/*t*BuOH (1 mL), RT, 30 min. [b] Solvent contained 0.1 M oxalic acid [c] After 5 min at RT, warmed to 40 °C for 4.5 h. [d] After 30 min at RT, warmed to 60 °C for 30 min. Bn = benzyl, Boc = *tert*-butoxy carbonyl.

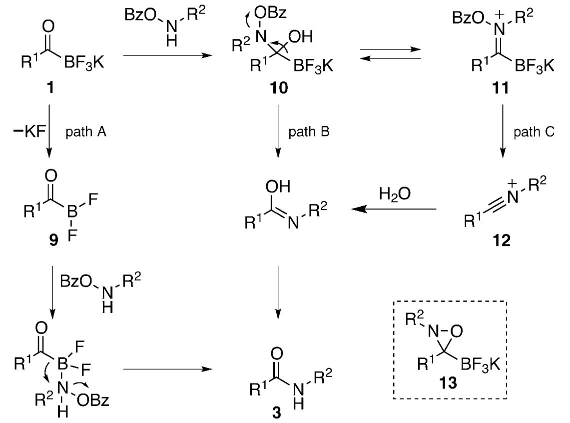
under the standard reaction conditions; however, the addition of oxalic acid (1 equivalent) to the reaction mixture resulted in clean conversion to amide **3u** within 1 hour. In contrast, α-ketoacids do not undergo ligation with **2e** under any conditions. As expected from previous investigations of reactions involving α-ketoacids, isoxazolidines were excellent substrates;[14] **4** reacted to give ketoester **5** in 88 % yield. In this case, LC/MS analysis of the reaction mixture indicated that an iminium adduct was formed as an intermediate; increasing the temperature of the reaction mixture to 40 °C caused a gradual decrease in the concentration of this species with simultaneous appearance of amide **5**. Intriguingly, the iminium adduct **7** was the only product formed from the reaction of isoxazolidine **6**; **7** did not transform into the expected amide even after heating the reaction mixture at 60 °C for 2 hours.

The acyltrifluoroborates appear to be far more reactive than α-ketoacids in amide-forming ligations with *O*-benzoyl hydroxylamines: reactions of acyltrifluoroborates were complete within minutes at 23 °C, whereas those of α-ketoacids generally required longer reaction times at higher temperatures. The relative rates of reaction of the two substrate classes was determined by conducting a competition reaction involving the acyltrifluoroborates and α-ketoacids (Scheme 2); these reactions were performed at 40 °C because the ketoacids do not react at all at room temperature. In a reaction with *O*-benzoyl hydroxylamine **2a**, acyltrifluoroborate **1b** was consumed 50 times faster than α-ketoacid **8a** (Scheme 2 a). In the case of the benzoyl derivatives **1h** and **8b**, only the product derived from the acyltrifluoroborate was observed in the crude reaction mixture (Scheme 2 b). The same result was observed in the competition reaction involving acyltrifluoroborate **1b** and α-ketoacid **8a** with branched hydroxylamine **2e** or isoxazolidine **4** (not shown). In the case of isoxazolidine **4**, rapid consumption of **4** by condensation to an iminium ion involving **1b** effectively prevented any reaction with the α-ketoacid.



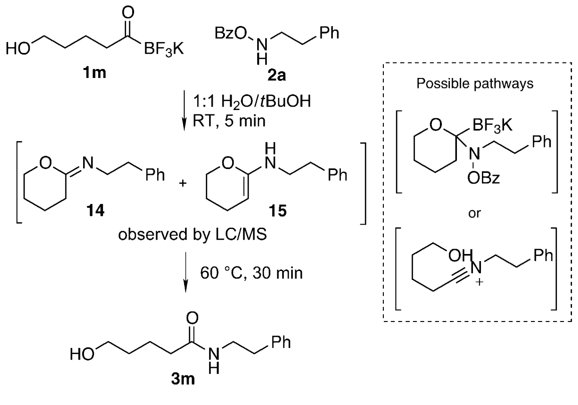
Scheme 2. Competition experiments between acyltrifluoroborates and α-ketoacids; percent values are relative integrations of the corresponding peaks in the LC/MS trace.

Three general pathways for amide formation can be envisioned (Scheme 3). In the first pathway, amide formation proceeds via acyldifluoroborane **9** (Scheme 3, path A) followed by 1,2-migration, a pathway, which parallels the known reactivity of organoboranes and *O*-benzoyl hydroxylamines to give amines.[15] Such reactions, however, generally require a fluorophile to break the strong B−F bond. In the other two pathways, the hydroxylamine would attack the electrophilic carbonyl group of the acyltrifluoroborate to form hemiaminal **10**, which would proceed to the amide by concerted elimination (path B) or via nitrilium **12** generated from iminium **11** (path C). The involvement of an oxaziridine intermediate, **13**, a species involved in the ligation of α-ketoacids and hydroxylamines, cannot be completely ruled out at this point.[16] It is also possible that hydrolysis of the trifluoroborate to a boronic acid occurs as part of the process, although such intermediates have not been observed to date.



Scheme 3. Possible mechanisms for the ligation of acyltrifluoroborates with *O*-benzoyl hydroxylamines.

Some observations made in the course of our studies suggest that path A is unlikely (Scheme 4). Firstly, the formation of iminium **7** under the ligation conditions demonstrates that interaction of the nucleophilic nitrogen atom with the carbonyl group can occur (Table 2, entry 6). Secondly, during the ligation of acyltrifluoroborate **1m**, two intermediates with m/z $[M+H]^+$ 204 were observed by



Scheme 4. Intermediates observed during ligation of **1m** and **2a**.

LC/MS analysis of the reaction mixture shortly after the reaction had begun; upon warming the reaction to 60 °C these intermediates were consumed, with concomitant formation of the expected amide **3m**. The most likely identity of these compounds is imine **14** and enamine **15**,[17] both of which are feasible products arising from intermediates involved in path B or C, and unlikely to be formed by a direct acyl migration as in path A. Although these observations cannot distinguish path B from C, they strongly suggest that the key interaction is between the hydroxylamine and the carbonyl carbon, and not between the hydroxylamine and the boron atom.

In summary, we have demonstrated that acyltrifluoroborates are extremely reactive acyl donors for ketoacid/hydroxylamine (KAHA) type ligations with *O*-benzoyl hydroxylamines and isoxazolidines. The reactions occurred within minutes at room temperature and are chemoselective, high yielding, and operationally simple. The use of acyltrifluoroborates permitted an expansion of the scope to include substrates that are poor partners in the ligation of α-ketoacids and *O*-benzoyl hydroxylamines. Combined with our efforts to develop more elaborately functionalized acyltrifluoroborates, we believe that this mechanistically distinct and remarkably facile variant of the KAHA ligation will find new applications.

Experimental Section

Ligation of **1f** and **2a** to form amide **3f**: Hydroxylamine **2a** (26.1 mg, 0.11 mmol) was dissolved in 1:1 $H_2O/tBuOH$ (1 mL) at RT. Acyltrifluoroborate **1f** (25.4 mg, 0.10 mmol) was added and the reaction mixture was shaken until the starting materials had dissolved. After 30 min, the reaction was diluted with EtOAc (20 mL), washed with 1:1 saturated aqueous $NaHCO_3$ solution/H_2O (2 × 5 mL), brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was triturated with hexane (2 mL), decanted, and dried to give amide **3f** as a white solid (24 mg, 90 % yield).

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Keywords: acyltrifluoroborates · amides · boron · cross-coupling · ligation

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